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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,462	05/05/2006	Makrina Savvidou	HO-P03236US0	8934

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
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07/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,462	SAVVIDOU ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims filed April 17, 2008 have been received and entered. Claims 2, 4-11 have been amended, while claims 3, 12-28 have been canceled. Claims 1-2, 4-10 and 11 are pending.

Election/Restrictions

Applicant's election without traverse of claims 1-2 and 4-11 in the reply filed on August 31, 2007 is acknowledged.

Claims 1-2, 4-10 and 11 are under consideration.

Information Disclosure Statement

The Information Disclosure Statement submitted on 4/17/2008 has been considered.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-10 and 11 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way

as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' arguments filed on April 27, 2008 have been fully considered but they are not fully persuasive. Applicants cite MPEP 2164.05(a) and argue that the post-filing date references of Kielstein *et al.* and Fang e*t al.* should not be used to demonstrate non-enablement since these they fail to provide evidence of what the skilled artisan would have known at the time of filing of this application in 2004.

Applicants' arguments have been fully considered but are not persuasive. Contrary to applicants argument Examiner has provided the state of art summarized by the references at the time of filing (Cooke et al Circulation. 2004 Apr 20;109(15):1813-8), before (Fard et al, Arterioscler Thromb Vasc Biol 2000; 20: 2039-2044 and Hamasaki et al Gen Pharmacol 1997; 28: 653-659) and after filing (Kielstein et al Am J Kidney Dis. 2005; 46: 186–202, Fang et al Hypertension 2006; 48: 724-729) of instant application that shows ADMA could be modulated in other disorders and therefore ADMA levels in not specific to any condition and cannot be relied as a marker for the diagnosis of IUGR or pre-eclampsia as set forth in the instant claims. MPEP 2164.05(a) also states "If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993)* an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animals were held nonenabled.

Therefore, it is evident from the teaching of the cited references filed before, and after filing of this application that show ADMA could be modulated in other disorders and conditions in pregnant woman of gestation stage of pregnancy from 4 to 25 weeks and therefore ADMA levels in any tissue or fluid sample cannot be

relied as a marker for a method of identifying whether or not a pregnant women is at risk of developing preeclampsia or fetus at risk of developing IUGR as set forth in the instant claims.

With respect to applicant's argument that intra-cerebral hemorrhage has been observed as a complication of pre-eclampsia (see, for example, Dai and Diamond), it is noted that Dai and Diamond only teaches that intracerebral hemorrhage (ICH) as an infrequent (emphasis added) complication in pregnant women with hypertension reported in one patient after 35 week of pregnancy (see abstract). In the instant case, none of the claim requires pregnant women at a stage of pregnancy beyond 25 weeks of gestation. In fact, it is generally known that plasma ADMA level can change rapidly in human temporally associated with alternation in endothelial vasodilator function. Additionally, ADMA accumulates in patients with renal failure (see Cooke et al, art of record). Fard et al (art of record) indicate that ADMA is synthesized in many tissues, including vascular endothelial cells, and is excreted by the kidney. Fard cite other references to show that elevated plasma levels have been found in patients with uremia in patient with chronic renal failure including conditions such as hypercholeterolemia and with atherosclerosis and type 2 diabetes mellitus after the ingestion of a high-fat meal (see page 2039, col.2). Thus, measuring level of ADMA at 35 weeks gestation would not be predictive of identifying risk for a women of developing pre eclampsia or her fetus at risk of developing IUGR by measuring level of ADMA from 4 to 25 weeks gestation. Therefore, Dai and Diamond can not support the applicant's assertion for the claimed method. Applicants cite references of Kumar et al, Damm et al and Antinori et al to assert that all the different conditions cited by examiner are associated with pre eclampsia in pregnant women (see page 6 and 7 of the arguments). However, references of Damm et al only teaches increased insulin resistance has been associated with serious pregnancy complications, such as gestational diabetes mellitas (GDM) and pre-eclampsia. The reference does not

disclose any nexus between GDM and pre eclampsia. Similarly, Kumar et al also indicate that pre eclasmpsia has been reported in only 16.7% of subclinical and ~43% of overt cases of hypothyrodism during the pregnancy (see page 57, col.2 bridging to page 58). There is no evidence on record that all GDM or hypothyroid patients would also have pre eclampsia. Given that elevated levels of ADMA is reported in GDM, thyroid function, it is apparent that diabetic or hypothyroidism patient with elevated ADMA level may or may not have pre eclampsia. Therefore, it is clear that elevated level of ADMA solely can not be predictive of pre eclampsia as other diseases such as obesity; fat intake, infection, diabetes, cardiovascular disorder and thyroid function may also influence the level of ADMA. Therefore, because of the art, as shown above, does not disclose how a single marker such as ADMA could be a reliable biomarker for identifying whether or not a pregnant women is at risk of developing pre eclampsia or fetus at risk of developing IUGR considering the fact that many other disorders also modulated the levels of ADMA. An artisan would have to perform undue experimentation to make and use the invention with reasonable expectation of success.

Applicants argue that there is no widely accepted model as of the cause of pre eclampsia. Applicants assert that that immunological or genetic alteration is likely to be responsible for pre eclampsia in all population and not just patient from developed countries (see page 7). In response, it is noted that contrary to applicants' assertion it is emphasized that it is not the examiner's conclusion, rather post filing art of López-Jaramillo (J Hypertens. 2005; 23(6): 1121-9 and references therein) while studying the role of ADMA in pre-eclampsia indicate "that among 22 not pregnant, 22 normal pregnant and 22 pre-eclampsia Andean women, no difference in the plasma levels of ADMA was detected". López-Jaramillo further cite another recent report to that evaluated 160 Colombian women and found no differences in plasma ADMA concentrations among women with pre-eclampsia and women with normal pregnancy [0.43 (0.31–0.56) μmol/l versus 0.42 (0.29–0.55) μmol/l; $P = 0.42$;

95% CI for difference between the medians, -0.09 to 0.04]. It is noted that the study included different ethnic groups (White, African, Indigenous, and Multiethnic) and ADMA concentrations were no different from the white women who developed PE (n = 12) and those from the rest of the case group [0.44 (0.28–0.55) μmol/l versus 0.43 (0.32–0.61) μmol/l; P = 0.83; 95% CI for difference between the medians, -0.15 to 0.13]. Based on these studies López-Jaramillo concludes that that the etiologic process that leads to a vascular endothelial dysfunction are different between populations from developed and developing countries. In any event, the teaching of López-Jaramillo clearly shows distinct population of pregnant women that are pre-eclampsia, but do not show elevated level of ADMA. Thus, without going into the details of reason for such a difference between different populations, it is reasonable to state that measuring ADMA levels in plasma or any other tissue or fluid of a pregnant women cannot be predictive biomarker for identifying whether or not pregnant women is at risk of developing pre eclampsia or fetus at risk of developing IUGR.

Applicants argument that the level of ADMA in women with or without pre-eclampsia and in the third trimester of pregnancy (as reported by Holden *et al.* and Lopez-Jamarillo et al.) has no bearing on whether or not ADMA make be used early in pregnancy as a predictor of the risk of developing pre-eclampsia (see page 10) have been fully considered but are not persuasive. In the instant case, Holden et al (art of record) clearly show the low levels of plasma ADMA levels in first, second, third and third trimester pregnancies complicated by pre eclampsia. The data in Holden clearly show that plasma ADMA level is higher in third trimester pregnancy is complicated with preeclampsia as compared to other groups of pregnant and non pregnant women (see figure 1B). Thus, it is apparent that if ADMA has any role in identifying pre eclampsia, it would and should remain elevated even in third trimester as per the teaching of Holden (see page 555, col. 1. para. 3), which is contrary to the finding of López-Jaramillo in Andean women (supra). Thus, it is

clear from the cited art that measuring the level of ADMA in a pregnant woman at any stage of pregnancy would not provide any reliable information of identifying whether or not a pregnant women is at risk of developing a multi factorial disease like pre eclampsia that involves different etiological processes leading to a vascular endothelial dysfunction in different populations. Based on fore going discussion it is apparent that instant claims are not enabled. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).* It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994),* citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).* Artisan could not predict, in the absence of proof to the contrary, that a method such as one claimed in the instant application would be efficacious in the identifying if a pregnant women at risk of developing pre-eclampsia or fetus at risk of developing IUGR. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of a single biomarker is unpredictable and specification fails to provide any guidance as to how the claimed method would have been consistently practiced.

Applicants argue that it is expected that the level of ADMA will be the same throughout all the fluids and tissues of a pregnant woman. As a result, any sample from a pregnant woman may be used in the claimed methods. Applicants assert that the concentration ADMA is homogenous throughout the body. As a result, it is expected that the concentration of ADMA is the same in any tissue or fluid sample taken from a pregnant woman. The Examiner has provided no evidence to contradict this. These arguments have been fully considered but are not persuasive because state of the art generally recognizes that the reference or control used for comparison with the test level of the AMDA level may vary, depending on aspect of

the invention being practiced. These values are subjective to sample population, other variables (age, gender, hormonal status, ethnicity, disease state), assay system and subjective to different interpretation by different artisan (see López - Jaramillo (J Hypertens. 2005; 23(6): 1121-9 and references therein). The specification contemplates that the sample typically comprises a body fluid of the woman. The sample is preferably a blood, plasma, serum or urine sample but may be amniotic fluid (see page 5, line 30-31 of the specification). Given that one of ordinary skill in the art was aware that ADMA to a greater extent is excreted in the urine (See Cooke et al, supra), one of skill in the art would have no reason to believe that measuring level of circulating ADMA level in serum, plasma or other fluids would be same as level of ADMA excreted in urine particularly it is known that only ~50% of ADMA is excreted in urine which may be further be complicated with subject having any underlying kidney or metabolic disorder. The reference of Cobb et al is not provided to demonstrate the actual concentration of ADMA in different tissue, rather it is provided to show that it was generally recognized in the art that relevant biomarker profiles of the diseased mouse spleen (septic mouse spleen) and the diseased mouse liver (septic mouse) liver contain different biomarkers (Table 1; page 2714, middle col. lines 2-8) and thus different level of expression is indicative of varying level of protein in those tissues. Given that levels of ADMA may vary depending on values that are subjective to sample population such as age, gender, hormonal status, ethnicity, disease state, it is thus unpredictable as to how one might use any reference marker profile comprising ADMA identified in a plasma in the analysis of a biomarker profile obtained from any other biological tissue or fluid sample derived from any other pregnant women with underlying kidney disease. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in any pregnant women of any ethnicity suffering from multiple chronic

disorders resulting in aberrant expression of ADMA level (see the discussion before). An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of identifying whether or not a patient is at risk of developing pre eclampsia by measuring the level of ADMA in any tissue or fluid without reasonable expectation of success.

In view of fore going arguments rejection to claims 1-2, 4-10 and 11 are maintained for the reasons of record.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 1-2, 4-11 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. The rejection to claim 1 is withdrawn as examiner would agree that claims are broad but are not indefinite.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4 and 5 remain rejected under 35 U.S.C. 102(b) as being anticipated by Holden et al (Am J Obstet Gynecol. 1998; 178(3):551-6).

Claims Interpretation: Instant claims are directed to a method of identifying whether or not a pregnant woman is at risk of developing pre-eclampsia or whether

or not her fetus is at risk of developing intrauterine growth restriction (IUGR) by measuring asymmetric dimethylarginine (ADMA) in the pregnant woman (4-25 weeks gestation) and determining whether or not the ADMA level is greater than 2.0 μmol/L. As recited these claims only requires determining whether or not the level of ADMA is greater than 2.0 μmol/L, therefore any level of less then 2.0 μmol/L of ADMA would also meet the claim limitation as such a subject would not a risk of developing pre eclampsia. Instant rejection is to the breath of the claim and not to the method of identifying if some one is pre disposed to any condition due to ADMA level.

Applicants arguments filed on 4/17/08 have been fully considered but are not persuasive. Applicants argue that claim 1 is limited to a method in which a level of ADMA of greater than 2.0 μmol/L is indicative of the woman being susceptible to pre-eclampsia. Applicants assert that the document by Holden *et al.* does not disclose such a method as Holden *et al.* only measured plasma ADMA concentrations up to 1.252 μmol/L.

Applicants' arguments have been fully considered but are not persuasive. In the instant case, contrary to applicants argument instant claims recite two method step (a) measuring ADMA in a pregnant women and (b) determining whether or not the ADMA is greater than 2.0 μmol/L, thereby determining whether or not the women is at risk of developing disorder. As recited instant claims are not limited to level of ADMA that is greater than 2.0 μmol/L, rather method merely requires determining whether or not the ADMA is greater than 2.0 μmol/L, a value of less then 2.0 μmol/L would be indicative of subject not at risk of developing the disorder particularly since claims are directed to a method of identifying whether or not a pregnant women is at risk of developing some condition (pre eclampsia). The cited reference of Holden et al teach a method of measuring plasma asymmetric dimethylarginine (ADMA) level in 145 pregnant women that included pregnancy of all stages (first to third –trimester). It is noted that Holden et al also determined

the level of ADMA which was not greater then 2.0 μmol/L meeting the limitation of the claims. Accordingly, Holden et al anticipate claims 1-2, 4 and 5.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Kisters et al J Hypertens. 2006 Jan;24(1):201; author reply 202. Fickling et al (Lancet., 1993, 342, 242-243).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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